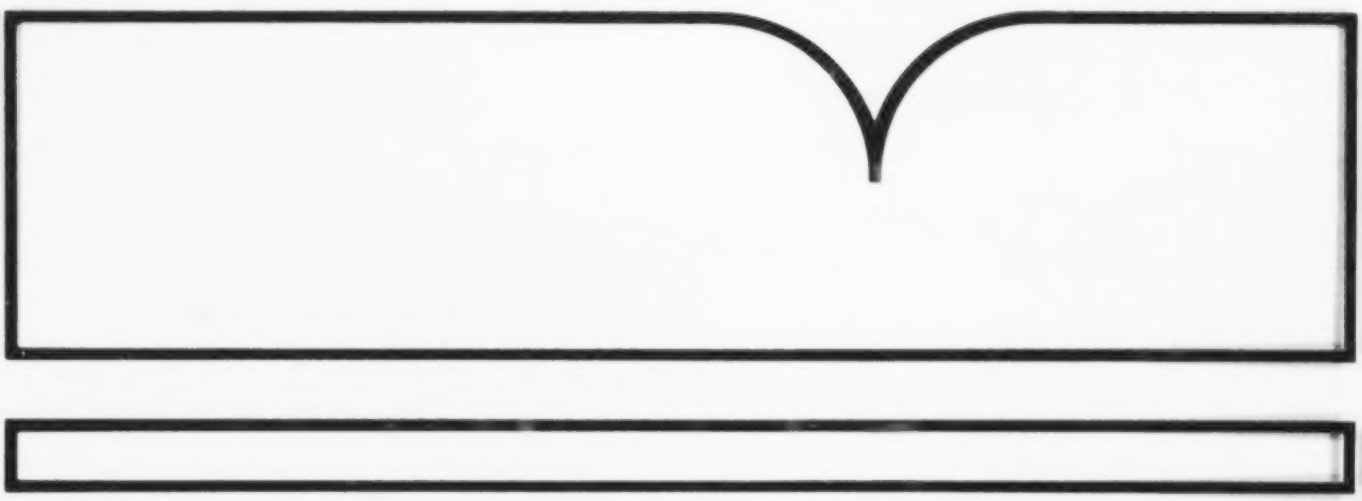
PB87-146262

Cadmium as a Respiratory Toxicant

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

Jan 87



U.S. Department of Commerce
National Technical Information Service
NTIS

PB87-146262

EPA/600/D-87/020
January 1987

CADMIUM AS A RESPIRATORY TOXICANT

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TECHNICAL REPORT DATA
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1. REPORT NO. EPA/600/D-87/020	2.
3. RECIPIENT'S ACCESSION NO. PB87 146262	
4. TITLE AND SUBTITLE CADMIUM AS A RESPIRATORY TOXICANT	5. REPORT DATE January 1987
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) E.C. Grose and J.A. Graham	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Health Effects Research Laboratory, RTP Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, NC 27711	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Health Effects Research Laboratory, RTP Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, NC 27711	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA-600/11
15. SUPPLEMENTARY NOTES	

16. ABSTRACT

Cadmium is a major respiratory toxicant as evidenced by numerous human and animal studies. Controlled animal inhalation studies provide supporting evidence to the associations observed in epidemiological studies that Cd has the potential to cause lung fibrosis, emphysema, cancer, and kidney disease after prolonged exposure. Shorter-term exposure studies indicate that mechanisms thought to be involved in several of these chronic disease states (especially fibrosis and emphysema) are acutely activated.Precisely assessing human risk is made difficult by uncertainties in the data base. Epidemiology studies were often confounded, inhibiting accurate estimation of quantitative exposure assessments and/or causative factor determinations. Most animal inhalation studies were conducted at exposure levels that were orders of magnitude above ambient. Nonetheless, the evidence of toxicity is sufficiently clear that a TLV has been set and the International Agency for Research on Cancer has named Cd as a Group B1 substance (probable human carcinogen). The risk to Cd exposure is enhanced by its chemical and physical properties that result in bioaccumulation. Thus, even a low level exposure over long periods of time would be expected to reach doses that could be toxic. Such a potential risk to the general human population can only be understood both qualitatively and quantitatively when investigators focus increased attention on improving methodologies.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC	19. SECURITY CLASS *(This Report)* UNCLASSIFIED	21. NO. OF PAGES 27
	20. SECURITY CLASS *(This page)* UNCLASSIFIED	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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INTRODUCTION

Trace amounts of cadmium (Cd) are found naturally in the environment in association with zinc and lead. Greater amounts enter the environment from the manufacture, use or disposal of Cd-containing products. As a dissipation metal, the amount of Cd produced is the amount that enters the environment. Six source categories of Cd air emissions in the United States have been designated to represent the most significant potential sources of risk to the public from Cd (Table 1). Cadmium produced by these industries are Cd metal, Cd oxide (CdO) dust and fumes, and Cd adsorbed to fly ash (1). Numerous secondary sources also contribute to the ambient Cd emissions (Table 1). Ambient air concentrations from most emission sources do not seem to pose much risk for the general population. However, individuals living near point sources may experience significant increases in Cd body burdens, which could increase their risk of acquiring Cd-induced diseases. Ambient air levels generally average in the 1-20 ng/m^3 level. In Cd production or industrial use areas, however, the air concentration can be 0.1 - 1.0 $\mu g/m^3$. Occupational exposure can range from 50 - 100 $\mu g/m^3$ and is usually from inhalation of CdO fumes or dust in processing plants. Additional exposure can be by inhalation of tobacco smoke. Intake of Cd from cigarettes ranges from 4 - 6 µg per 2 packs smoked per day, therefore blood and organ levels of Cd are invariably higher in smokers (2).

Cadmium is widely distributed in the body and is highly cumulative. Cadmium is not metabolized as are some metals, and therefore is chemically active only as the divalent cation. It does not form stable alkyl

or other toxicologically important organometallic compounds. However, like mercury and lead, Cd has a strong affinity for donor atoms such as S,P,and N and thus forms stable complexes on side chains of proteins, purines, pteridines, and porphyrins containing phosphate, cysteinyl or histidyl residues (3). Cadmium compounds vary in their water solubility. The sulfate, nitrate and halogen salts are fairly soluble, while the carbonates, hydroxides, and oxides are considered insoluble. As far as it is documented, Cd plays no beneficial or essential biological role in man or animals.

Toxic effects due to Cd inhalation may occur because the metal alters biochemical, immunological or structural relationships in the cells. Metals may affect cell permeability by producing structural changes in the cell membrane. Inhibition of intracellular enzyme activity may also result from metal binding, which can occur at the active site, at adjacent sites or distant sites causing functional impairment through competitive and non-competitive inhibition or protein conformational changes. Cadmium may also impair cellular function by interfering with biologically essential metals, such as zinc and selenium. Binding to sulfhydryl groups, like glutathione (GSH), could lead to depletion of endogenous GSH or inhibition of GSH-dependent enzymes, thereby altering critical metabolic functions or increasing membrane permeability.

DEPOSITION, TRANSPORT, AND DISTRIBUTION

The lung is the first target organ after inhalation of Cd fumes or dust at exposure levels than can be encountered occupationally,

resulting in localized respiratory tract irritation and acute pneumonitis. Death, which is usually caused by pulmonary edema, may occur following excessive acute exposure. Chronic exposure to Cd can result in emphysema, bronchitis or fibrosis. The kidney and liver can also become main sites of Cd accumulation following any type of chronic exposure (4). The kidney accumulates higher concentrations of Cd at low exposure doses, but the liver concentration may exceed that in the kidney at high dose levels. Renal disease following chronic Cd exposure is characterized by tubular atrophy, proteinuria, and edema. The half-life of Cd in man is estimated to be 19-38 yr, and in animals (rats, mice and dogs) the half-life is approximately 200-300 days. Based on life spans, these estimates are roughly comparable.

The relative amount of Cd inhaled and absorbed in the respiratory tract is dependent on the physical and chemical characteristics of the metal, the most important being the particle size, hydroscopicity, and solubility. In man approximately 10-25% of inhaled particles with a mass median aerodynamic diameter (MMAD) of < 0.3 μm will deposit primarily in the pulmonary region with reduced percentages deposited in the tracheobronchial and naso-pharyngeal regions (5,6). In various animal species, 10-50% of similarly sized particles will deposit in the various lung regions (7). Specifically, it was reported that 14% of CdO and 17% of $CdCl_2$ aerosols were deposited in the pulmonary region of rats (8). Whereas, < 10% of particles with an MMAD of >5.0 μm will be deposited in the pulmonary region of any species. The absorption of deposited particles into the systemic circulation is also dependent on solubility

and particle size. Approximately 20-50% of all deposited Cd is absorbed by man (2,9). Animal studies report 10-60% absorption of deposited Cd (8,10).

A minor, secondary source of Cd body burden after inhalation is the absorption of Cd through the gastrointestinal tract. Some of the inhaled Cd is cleared from the respiratory tract via mucociliary clearance mechanisms, then swallowed and ingested. This method of absorption accounts for 5-6% of the body burden. In this chapter, however, we will concentrate on respiratory tract absorption.

Independent of the route of exposure, transport of Cd in the body is via the blood. In humans, the half-life of Cd in the blood is 6 months (2). It has been suggested that Cd-carrier proteins in the blood (11) are responsible for this transport, although these proteins have not been isolated. From the liver, the Cd is transported to the kidney bound to metallothionein, an inducible, metal binding protein (12). Metallothionein has been shown to be induced in lung, liver, kidney, heart, stomach, small intestine, pancreas, thyroid, and spleen (13,14). Metallothionein initially acts in a protective capacity by binding and storing free Cd. But once the binding and storage capacities are saturated, the Cd-metallothionein complex or the subsequent release of Cd from the saturated systems can cause toxicity (15).

After acute inhalation, the greatest proportion (30%) of Cd that is absorbed is transported to the kidney; approximately 20% is distributed to the liver. Other organs of distribution include the lungs, testes, pancreas, spleen and endocrine organs. Concentrations of Cd in bone,

brain and muscle are negligible. Following chronic exposure, the greatest proportion of Cd is found in the liver rather than the kidney because of metallothionein synthesis (16). Excretion of Cd is mainly through the feces because of the low GI absorption. Cadmium excreted in the urine of non-smokers is approximately 4 ug/day following low-level chronic exposure.

HUMAN EXPOSURE

Acute exposure to Cd is usually by occupational exposure. The primary clinical feature of acute Cd toxicity in the lung is pneumonitis, with pulmonary congestion and edema. Inhalation of 1.0 $\mu g/m^3$ for 8 hr can result in clinical symptomology. Exposure to 5.0 $\mu g/m^3$ for 8 hr can be fatal, usually due to chronic respiratory insufficiency (2). In deaths due to Cd fume inhalation, lungs are enlarged, dark, and congested. Microscopic evaluation of the tissue shows cell degeneration, loss of bronchiolar epithelia, diffuse congestion of alveolar capillaries with intra-alveolar proteinaceous exudate, shed alveolar lining cells and an increase in alveolar macrophages (2). However, workers exposed to 13-89 μg Cd/m^3 for 12 hr have survived the exposure, but did develop bronchitis and emphysema (17). At lower concentrations of 1.0-100 ng/m^3 over an 8 hr period, no acute symptoms appear to occur. Metal (Cd) fume fever has also been reported in silver solderers (18). Immediate symptoms included eye irritation and headache; 9 hr after exposure myalgia, chills fever, headache, backache, chest tightness, malaise, and shortness of breath were reported. Significant decreases in vital capacity, forced expiratory volume at 1 sec and diffusing capacity

were observed. Most symptoms resolved within 48 hr with no permanent lung damage apparent.

Chronic respiratory effects have been observed mainly in individuals exposed to Cd in a consistent manner over a period of time exceeding 2 yr in either an occupational or ambient setting. The primary clinical symptoms are emphysema and chronic bronchitis (17). Postmortem examination of the lungs shows a diffuse centrilobular emphysema. It has also been suggested that Cd inhalation can cause fibrosis (19). Chest X-rays showed that 10 of 17 workers exposed to Cd for 26-40 yr had evidence of slight to moderate fibrosis. Although these findings suggest some relationship between exposure to Cd and the occurence of chronic respiratory disease, studies focusing on the role of Cd in producing lung disease other than cancer provide little data that implicate Cd in the etiology of lung disease for the general population. Although autopsy data have shown a higher concentration of Cd in the lungs of people who die from emphysema, a controlled study with smoking as a confounding factor has not been reported. The mechanistic cause of emphysematous or fibrotic changes brought about by Cd are still under investigation. Biochemical changes related to disease occurence have been reported. There is some controversy regarding the effect of Cd exposure on alpha-1-antitrypsin levels in human blood. Rat studies link Cd-induced inhibition of serum alpha-1-antitrypsin (AT) to the pathogenesis of emphysema (20,21), however, a human study by Bernard et al (22) did not indicate any reduction in alpha-1-AT levels in workers exposed excessively to Cd and showing overt signs of Cd toxicity.

Epidemiolgical studies of Cd production workers have shown an increased risk of lung cancer from exposure to Cd. Lemen et al 1976 (23) reported a concentration-response relationship between chronic Cd exposure and lung cancer in Cd production plant workers who had been exposed for a minimum of 2 yr. Exposures to Cd fumes ranged from 0.04 - 6.9 mg/m^3; exposure to Cd dust averaged 17.23 mg/m^3. Other work stations in the plant were reported to have air Cd concentrations less than 1.0 mg/m^3. A significant excess in lung cancers (12 observed versus 5.1 expected) and a significant excess in total neoplasms (27 observed versus 17.5 expected) were reported. One problem with this study, however, is the reported presence of other metals in the Cd plant, including zinc, arsenic and lead. Any conclusions drawn from this study regarding the carcinogenic potential of Cd should be made with caution owing to the presence of these other metals. A recent follow-up study (24) to Lemen and coworkers showed a significant increased risk of lung cancer in Cd smelter workers. Data of Cd concentrations in urine suggested a population highly exposed to Cd. A concentration-response relationship was observed between cumulative exposure to Cd and mortality from lung cancer. Two potential confounding factors, arsenic and smoking, were analyzed and it was found that, in combination or alone, neither of these factors could have accounted for the excessive lung cancer observed. The reader is referred to other epidemiology studies of Cd inhalation and risk of lung cancer that have been reported (25,26,27,28). However, the data presented in these studies were not conclusive or the studies were flawed by confounding factors that were

not explained or by small sample sizes. Although the weight of evidence implicating Cd as a lung carcinogen is somewhat limited, Cd has been classified as a Group B1 substance and as such is considered to be a "probable" human carcinogen (29).

Renal effects caused by inhalation of Cd are seen in the general population as well as the workforce. Thus the kidney is considered to be the primary target organ of chronic Cd exposure (30). Renal dysfunction, characterized by proteinuria, is the most common toxic effect caused by Cd inhalation (31). Aminoaciduria, glycosuria, and more severe kidney damage can occur if exposure is repetitive over time. Irreversible kidney damage occurs when the concentration of Cd in the renal cortex is in excess of 200 µg/gm wet weight. When ambient air concentrations exceed 1000 ng/m^3, effective concentrations of Cd accumulate in the kidney; at 100 ng/m^3 notable concentrations accumulate; and less than 10 ng/m^3 in the ambient air does not cause appreciable accumulation in the renal cortex.

ANIMAL STUDIES

Most human lung specimens are studied at autopsy, when age, other disease entities, and lack of adequate exposure history can be confounding factors. Therefore animal research can give us insight into disease processes that cannot be studied in humans. Although numerous oral and *in vitro* exposure studies have been conducted, this discussion will focus on pulmonary exposures. An acute 2 hr exposure to an aerosol of 10 mg/m^3 $CdCl_2$ has been reported to cause peribronchiolar fibrosis (32). The resulting lung burden of Cd was 1-2 µg/gm wet weight.

Initially a multifocal, inflammatory lesion was observed at the juction of the terminal bronchioles and the alveoli. By day 2, sloughing of Type I cells was predominant. Multifocal hyperplasia of Type II cells was evident. Alveolar septa appeared thickened by an interstitial cellular infiltrate, which was predominantly monocytic. Lymphocytes, polymorphonuclear leukocytes, and excess alveolar macrophages were evident in the alveolar spaces. By days 3 and 4, the alveoli appeared to be completely lined with Type II cells, and there was a marked increase in interstitial cells. Following days 4 and 5, the Type II cells were less evident and a renewal of Type I cells had occurred. The number of interstitial monocytes had decreased but a proportional increase in the number of fibroblasts was observed. After 7-10 days, the epithelial lining appeared normal. The number of fibroblasts had dramatically increased and were associated with an increase in interstitial collagen. Following day 10, cell proliferation had basically stopped, but there was a marked increase in interstitial collagen near the respiratory bronchioles. By day 21, collagen fibrils had become more densely aggregated and formed distinct mature bundles. The authors suggested that the peribronchiolar localization of the fibrosis is the probable cause of centriacinar emphysema in humans resulting from acute Cd fume inhalation. However, although fibrosis and emphysema may occur in humans concurrently, there is no conclusive evidence that emphysema can be caused by preexisting fibrosis. Other authors have also reported the centriacinar Type I/Type II cell response following Cd inhalation (33,34,35).

The effect of Cd exposure on pulmonary immunity has also been studied. Studies have shown that exposure of mice to $CdCl_2$ followed by aerosols of Streptococcus sp. caused an increased mortality in $CdCl_2$-exposed animals (36). Contrary findings, however, have been reported following exposure to CdO followed by influenza virus (37). The combination of influenza and CdO produced less deaths than did influenza alone. Thus it appears that CdO exerted a protective influence when the mice were exposed to influenza virus. The reason for this difference is unknown, but perhaps Cd affects the mechanisms of antibacterial defenses differently from antiviral defenses. For example, because Cd binds to DNA (42) and inhibits DNA-dependent RNA-polymerase (43) it is possible that Cd could indirectly affect viral transcription by blocking host protein synthesis. Alveolar macrophages which are involved in defense against streptococcus and influenza virus are affected by Cd exposure. Cadmium causes an influx of alveolar macrophages and either an increase or a decrease in phagocytosis, depending upon the experimental design and perhaps other factors as well (38,39,40,41).

Muhle and coworkers (40) exposed Wistar rats up to 180 days to concentrations of 6.9 and 7.4 $\mu g/m^3$ $CdCl_2$ and CdO, respectively. After 66 days of exposure, an increase in phagocytic activity of the alveolar macrophages was observed with a concurrent increase in acid phosphatase (a lysosomal enzyme) activity. After 180 days of exposure, the activation of the alveolar macrophages was even more pronounced. This increase in acid phosphatase activity (if it is an index of a more

general increase in lysosomal enzymes) may play a role in proteolysis in the lung, thus facilitating the development of emphysema. Exposure of rats to 1-2 μg/gm wet weight $CdCl_2$ per lung induced a five fold increase in total lung cells 4 days after exposure (36). A peak of polymormonuclear leukocytes (PMNs) was observed 3 days postexposure, but by 4 days postexposure the predominant cell was the alveolar macrophage. Also at 4 days an increase in lymphocytes was observed. Ten days after exposure, the alveolar macrophage population was still elevated, but all other cell populations had returned to normal. This biphasic inflammatory response is not unusual in lung injury. Correlating these data with previously published data (33), the results suggest that the peak of PMNs coincides with Type 1 cell necrosis and the predominance of alveolar macrophages corresponds with the repair process of Type 2 cell proliferation.

Pulmonary biochemical changes have been reported which suggest both a direct and indirect action of Cd on the lung. A significant decrease in pulmonary aryl hydrocarbon hydroxylase (AHH) activity has been reported 2 days after exposure to $CdCl_2$ and it did not return to normal until 7 days postexposure (44). The effect appeared to be indirect because a similar in vitro exposure of microsomes did not produce the same results. The indirect action of Cd on AHH activity could be an effect on the resident cells or an alteration in the synthesis or degradation of the enzyme. Other biochemical changes following acute Cd toxicity have been reported. Total lipid content, glucose-6-phosphate dehydrogenase, lactate dehydrogenase, malate dehydrogenase, glutathione

(GSH) selenium-peroxidase and GSH reductase and superoxide dismutase activities, and total DNA of lung homogenates and lung weights have significantly increased after Cd exposure (34,35,45).

Pulmonary fibrosis is one of the pathological manifestations of chronic Cd exposure. Animal studies have offered various mechanistic explanations of this disease process. A recent report suggests that increased activity of lung enzymatic markers of connective tissue biosynthesis, namely prolyl hydroxylase and lysyl hydroxylase, correlated with the proliferation of interstitial fibroblasts after $CdCl_2$ exposure (46). The connection between the inflammatory response and connective tissue biosynthesis has also been suggested to have a role in fibroplasia (47). It is possible that both macrophages (48,49) and neutrophils (50) may produce factors that can activate the synthesis of connective tissue macromolecules or that are mitogenic for fibroblasts. Thus the fibrosis evident after Cd exposure may be the result of the influence of the proliferation of inflammatory cells.

Animal studies also provide evidence that Cd is a lung carcinogen. Various lung cancers were produced in rats exposed to 12.5, 25 and 50 $\mu g/m^3$ $CdCl_2$ continously for 18 months (51,52). The incidence of lung cancers was 71% in the 50 $\mu g/m^3$ group; 53% in the 25 $\mu g/m^3$ group; and 15% in the 12.5 $\mu g/m^3$ group. There was a concentration-dependent increase in primary lung carcinomas, including adenocarcinomas, squamous cell carcinomas, combined adenocarcinomas and squamous cell carcinomas and mucoepidermoid carcinomas. No primary lung tumors were found in the control group.

SUMMARY

Cadmium is a major respiratory toxicant as evidenced by numerous human and animal studies. Controlled animal inhalation studies provide supporting evidence to the associations observed in epidemiological studies that Cd has the potential to cause lung fibrosis, emphysema, cancer, and kidney disease after prolonged exposure. Shorter-term exposure studies indicate that mechanisms thought to be involved in several of these chronic disease states (especially fibrosis and emphysema) are acutely activated.

Precisely assessing human risk is made difficult by uncertainties in the data base. Epidemiology studies were often confounded, inhibiting accurate estimation of quantitative exposure assessments and/or causative factor determinations. Most animal inhalation studies were conducted at exposure levels that were orders of magnitude above ambient. Nonetheless, the evidence of toxicity is sufficiently clear that a TLV has been set and the International Agency for Research on Cancer has named Cd as a Group B1 substance (probable human carcinogen). The risk to Cd exposure is enhanced by its chemical and physical properties that result in bioaccumulation. Thus, even a low level exposure over long periods of time would be expected to reach doses that could be toxic. Such a potential risk to the general human population can only be understood both qualitatively and quantitatively when investigators focus increased attention on improving methodologies. Particular attention should be applied to developing improved exposure assessments in epidemiology, developing and applying more novel, sensitive diagnostic procedures for human studies, and conducting chronic animal experimen-

tation with exposure regimens that closer approximate the human experience.

REFERENCES

1. Radian Corp. Background Information Document For Cadmium Emission Sources. EPA Report No. 68-02-3818, (1985).

2. L. Friberg, M. Piscator, G.F. Nordberg, and T. Kjellstrom, Metabolism, in Cadmium in the Environment, CRC Press, Cleveland, OH, 1974, p. 27.

3. B.L. Vallee and D.D. Ulmer, Biochemical effects of mercury, cadmium and lead, Ann. Rev. Biochem., 41, (1972), 91.

4. P.B. Hammond and L.P. Beliles, Metals, in J. Doull, C.D. Klaassen, and M.O. Amdur (Eds.), Casarett and Doull's Toxicology: The Basic Science of Poisons, Macmillan Publishing Co. Inc., New York, NY, 1980, p.432.

5. J. Heyder, Studies of Particle Deposition and Clearance in Humans, presented at the Symposium for Problems of Inhalatory Toxicity Studies, Federal Health Office, Institute for Drugs, Berlin, Germany, 1984.

6. M. Lippman and B. Altschuler, Regional Deposition of Aerosols, in E.F. Aharonson, A. Ben-David, and M.A. Klingberg (Eds) Air Pollution and the Lung, J. Wiley and Sons, NY, (1976), p. 25.

7. O.G. Raabe, M.A. Al-Bayati, S.V. Teague, and A. Rasolt, Regional deposition of inhaled monodisperse coarse and fine aerosol particles in small laboratory animals, Proceedings of the Sixth International Symposium on Inhaled Particles, Cambridge, UK, 1985, in press.

8. G. Oberdorster, H.P. Baumert, D. Hochrainer, and W. Stoeber, The clearance of cadmium aerosols after inhalation exposure. Amer. Ind. Hyg. Assoc. J., 40, (1979), 443.

9. C.-G. Elinder, T. Kjellstrom, L. Friberg, B. Lind, and L. Linnman, Cadmium in kidney cortex, liver and pancreas from Swedish autopsies, Arch. Environ. Health, 313, (1976), 292.

10. M. Boisset, F. Girard, J. Godin, and C. Boudene, Cadmium content of lung, liver, and kidney in rats exposed to cadmium oxide fumes, Int. Arch. Occup. Environ. Hlth., 41, (1978), 41.

11. M. Nordberg, Studies on metallothionein and cadmium, Environ. Res., 15, (1978), 381.

12. D.R. Johnson and E.C. Foulkes, On the proposed role of metallothionein in the transport of cadmium, Environ. Res., 21, (1980), 360.

13. M. Sato and Y. Takizawa, Cadmium-binding proteins in human organs, Tox. Lett., 11, (1982),269.

14. S. Onosaka and M.G. Cherian, The induced synthesis of metallothionein in various tissues of rat in response to metals. I. Effect of repeated injection of cadmium salts, Toxicology, 22, (1981), 91.

15. M.G. Cherian, Metabolism of orally administered cadmium-metallothionein in mice, Environ. Health Persp. 28, (1979), 127.

16. G.F. Nordberg, Cadmium metabolism and toxicity. Experimental studies on mice with special reference to the use of biological materials as indices of retention and the possible role of metallothionein in transport and detoxification of cadmium, Environ. Physiol. Biochem., 2, (1972), 7.

17. H. Holden, A mortality study of workers exposed to cadmium fumes, Proceedings of the 2nd International Cadmium Conference, Met. Bull. Ltd., Worchester Park, England, (1980), p. 211.

18. J.S. Johnson and K.H. Kilburn, Cadmium induced metal fume fever: Results of inhalation challenge, Amer. J. Ind. Med., 4, (1983), 533.

19. Smith, T.J., Petty, T.L., Reading, J.C., and Lakshminarayan, S. Pulmonary effects of chronic exposure to airborne cadmium. Amer. Rev. Respir. Dis. 114, (1976), 161.

20. P. Chowdhury, D.B. Louria, L.W. Chang and P.L. Rayford, Cadmium-induced pulmonary injury in mouse: A relationship with serum antitrypsin activity, Bull. Environ. Contam. Toxicol., 28, (1982), 446.

21. P.Chowdhury, L.W. Chang, R.C. Bone, and P.L. Rayford, Potentiation of Cd-induced pulmonary injury in alpha-1-antitrypsin suppressed rats, Environ. Res., 30, (1983) 313.

22. A. Bernard, H.A. Roels, J.P. Buchet, P.L. Masson, and R. Lauwerys, Alpha-antitrypsin level in workers exposed to cadmium, in S.S. Brown (Ed) Clinical Chemistry and Chemical Toxicology of Metals, Elsevier, Amsterdam, 1977, p. 161.

23. R.A. Lemen, J.S. Lee, J.K. Wagoner, and H.P. Blejer, Cancer mortality among cadmium production workers, Ann. N. Y. Acad. Sci., 271, (1976), 273.

24. M.J. Thun, T.M. Schnorr, A.B. Smith, and W.E. Halperin, Mortality among a cohort of U.S. cadmium production workers: an update, J. Natl. Cancer Inst., 74, (1985), 325.

25. M.O. Varner, Updated epidemiological study of cadmium smelter workers. Presented at the Fourth International Cadmium Conference, (1983).

26. T. Sorahan and J.A.H. Waterhouse, Mortality study of nickel-cadmium battery workers by the method of regression models in life tables, Br. J. Ind. Med., 40, (1983), 293.

27. K. Andersson, C.G. Elinder, C. Hogstedt, and T. Kjellstrom, Mortality among cadmium workers in a Swedish battery factory, Presented at the Fourth International Cadmium Conference, (1983).

28. B.G. Armstrong and G. Kazantzis, A mortality study of cadmium workers in England: Report to the International Lead Zinc Research Organization. TVC Centenary Institute of Occupational Health, London School of Hygiene and Tropical Medicine, London, England, 1983.

29. U.S.Environmental Protection Agency, Updated Mutagenicity and Carcinogenicity Assessment of Cadmium. EPA 600/8-81/023, (1981).

30. R. Lauwreys, D. Stanescu, H. Roels, and J.P. Buchet, Effects of cadmium on the lungs, Proceedings of the 1st International Cadmium Conference, Met. Bull. Ltd., Worchester Park, England, (1978), p. 201.

31. H.A. Roels, R.R. Lauwerys, J.P. Buchet, A. Bernard, D.R. Chettle, T.C. Harvey, and I.K. Al-Haddad, In vivo measurement of liver and kidney cadmium in workers exposed to this metal: Its significance with respect to cadmium in blood and urine, Environ. Res., 26, (1981), 217.

32. P.A. Dervan and J.A. Hayes, Peribronchiolar fibrosis following acute experimental lung damage by cadmium aerosol, J. Path., 128, (1979), 143.

33. R.H. Strauss, K.C. Palmer, and J.A. Hayes, Acute lung injury induced by cadmium aerosol. 1. Evolution of alveolar cell damage, Amer. J. Path., 84, (1976), 561.

34. E.C. Grose, J.H. Richards, R.H. Jaskot, M.G. Menache, J.A. Graham, and W.C. Dauterman, A comparative study of the effects of inhaled cadmium chloride and cadmium oxide: Pulmonary response, Accepted J. Tox. Environ. Health, (1986).

35. J.A. Hayes, G.L. Snider, and K.C. Palmer, The evolution of biochemical damage in the rat lung after acute cadmium exposure, Amer. Rev. Respir. Dis., 113, (1976), 121.

36. D.E. Gardner, F.J. Miller, J.W. Illing, and J.M. Kirtz, Alterations in bacterial defense mechanisms of the lung induced by inhalation of cadmium, Bull. Europ. Physiopath. Resp., 13, (1977), 157.

37. C. Chaumard, A.M. Quero, G. Bouley, F. Girard, Cl. Boudene, and A. German, Influence of inhaled cadmium microparticles on mouse influenza pneumonia, Environ. Res., 31, (1983), 428.

38. S. Asvadi and J. A. Hayes, Acute lung injury induced by cadmium aerosol. II. Free airway cell response during injury and repair, Am. J. Pathol., 90, (1978), 89.

39. B.J. Greenspan and P.E. Morrow, The effects of in vitro and aerosol exposures to cadmium on phagocytosis by rat pulmonary macrophages, Fund. Appl. Tox., 4, (1984), 48.

40. H. Muhle, F. Otto, D. Hochrainer and H.P. Baumert, Effect of cadmium aerosol inhalation on alveolar macrophages of the rat, Proceedings of the Aerosols Sci., Med. Tech. Biomed. Influence Aerosol Conference, Germany, 1980.

41. G. Lemercier and S. Mavet, Effet de la depression et de la stimulation du systeme phagocytaire mononuclee sur l'evolution de la grippe experimentalede la souris, Ann. Microbiol. 130B, (1979), 235.

42. I. Sissoef, J. Grisvard, and E. Guille, Localisation preferentielle du cadmium sur des sequences iteratives de l'ADN isole de cultures de Crowngall du tabac, C.R. Acad. Sci. Paris, 280D, (1975), 2389.

43. H.A. Hildago, V. Koppa, and S.E. Bryan, Cadmium binding in nuclei: Effect on RNA polymerase in rat liver following metal challenge, Fed. Proc., 35, (1976), 1415.

44. K.C. Palmer, S.M. Naseem, J.A. Hayes, and P.V. Tishler, Lung aryl hydrocarbon hydroxylase: Inhibition following cadmium chloride inhalation, Environ. Res., 32, (1983), 432.

45. J.S. Bus, A. Vinegar and S. M. Brooks, Biochemical and physiologic changes in lungs of rats exposed to a cadmium chloride aerosol, Am. Rev. Respir. Dis., 118, (1978), 573.

46. C.O. Chichester, K.C. Palmer, J.A. Hayes and H.M. Kagan, Lung lysyl oxidase and prolyl hydroxylase: Increases induced by cadmium chloride inhalation and the effect of B-aminopropionitrile in rats, Am. Rev. Respir. Dis., 124, (1981), 709.

47. C.E. Sampson, C.O. Chichester, J.A. Hayes, and H.M. Kagan, Alterations in collagen biosynthesis and in metallothionein in lungs of rats acutely or repeatedly exposed to cadmium chloride aerosol, Am. Rev. Respir. Dis., 129, (1984), 619.

48. P.B. Bitterman, S.I. Rennard, and G.W. Hunninghake, Human alveolar macrophage growth factor for fibroblasts: Regulation and partial characterization, J. Clin. Invest., 70, (1982), 806.

49. P. Lehtinen and E. Kulonen, Subcellular targets of the soluble SiO_2-liberated macrophage factors in experimental granulation tissue, Biochim. Biophys. Acta., 564, (1979), 132.

50. S.L. Myers and C.W. Castor, Connective tissue activation: XV Stimulation of glycosaminoglycan and DNA synthesis by a polymorphonuclear leukocyte factor, Arthritis. Rheum., 23, (1980), 556.

51. S. Tanenaka, H. Oldiges, H. Konig, D. Hochrainer, and G. Oberdorster, Carcinogenicity of cadmium chloride aerosols in W rats, J. Nat. Cancer Inst., 70, (1983), 367.

52. H. Oldiges, D. Hochrainer, S. Takenaka, G. Oberdorster and H. Konig, Lung carcinomas in rats after low level cadmium inhalation, Tox. Environ. Chem., 9, (1984), 41.

TABLE 1

Sources of Cd in the Ambient Air[a]

Primary	Secondary
Primary Cd Smelters	Primary Copper Smelters
Primary Lead Smelters	Secondary Copper Smelters
Primary Zinc/zinc oxide Smelters	Secondary Lead Smelters
Municipal Waste Incinerators	Secondary Zinc Smelters
Sewage Sludge Incinerators	Iron and Steel Facilities
Cd Pigment Manufacturers	Cd Stabilizer Manufacturers
	Ni/Cd Battery Manufacturers
	Welding Industry

[a]From Radian Corp. Background Information Document for Cadmium Emission Sources. EPA Report No. 68-02-8818, 1985.